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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,512	05/02/2005	Maria Rosa Gasco	GASCO ET AL - 1PCT	4539

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,512	GASCO ET AL.	
	Examiner	Art Unit	
	GIGI HUANG	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4 and 7-21* is/are pending in the application.

4a) Of the above claim(s) *8-10 and 14-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,7 and 11-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/13/2005, 1/11/2006, 5/3/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I and triamcinolone in the reply filed on November 3, 2008 is acknowledged. The traversal is on the grounds that the nanoparticles of Anselem et al. are not the solid lipid nanoparticles of the claims. This is not found persuasive because the arguments are to how the particles are made which goes to the method of making but all the claims are unified by a solid lipid nanoparticle which is taught by Amselem et al. which shows that there is no inventive step.

The requirement is still deemed proper and is therefore made FINAL.

Upon examination, the drug election is withdrawn.

Status of Application

2. Applicant has elected Group I in response to restriction requirement and elected triamcinolone for the examination. Upon examination, the drug election is withdrawn.

Due to restriction, based on election of Group I, claims 8-10 and 14-21 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

3. Claims 2-4, 7-21 are pending.

4. Claims 2-4, 7, 11-13 are present for examination at this time.

Claim Objections

5. Claims 12-13 are objected to because of the following informalities: it appears the phrase "containing to" is meant to be "containing". Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 2-4, 7, 11-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for bacterial or fungal endophthalmitis, viral retinitis, vitreoretinopathy, toxoplasmosis, uveitis, tumors, vascular diseases, .diabetic retinopathy, age-related macular degeneration, glaucoma, does not reasonably provide enablement for all ophthalmic diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8

USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a method of treatment for all ocular diseases with solid lipid nanoparticles containing a pharmacologically active substance. Thus, the claims taken together with the specification imply that all ocular diseases can be treated with solid lipid nanoparticles containing a pharmacologically active substance.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the art as addressed by Newman (Hereditary Optic Neuropathies: From the Mitochondria to the Optic Nerve) teaches the issues and etiology of hereditary optic neuropathies, specifically Leber's Hereditary Optic Neuropathy (LHON). This is a maternally-inherited disease that results in a permanent loss of central vision as a result of optic nerve degeneration, rod dystrophy, and abnormal changes of blood vessels in the area. The loss of vision is permanent with no known cure or treatment. As a result, the unpredictability is high as there is no known means of treatment for LHON.

Moss (Leber's Congenital Amaurosis) teaches that this degenerative disease with a premature degeneration of the retinal cells is genetically passed and there is currently no treatment for the condition.

Also, as addressed with the Mayo Clinic (Stargardt's disease: Can it be treated?) there is no treatment for this inherited form of macular degeneration.

(5) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for the concept of treating bacterial or fungal endophthalmitis, viral retinitis, vitreoretinopathy, toxoplasmosis, uveitis, tumors, vascular diseases, .diabetic retinopathy, age-related macular degeneration, and glaucoma with solid lipid nanoparticles containing a pharmacologically active substance.

However, the specification does not provide for a method of treatment for all ocular diseases with solid lipid nanoparticles containing a pharmacologically active substance.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the lack of treatment of hereditary optic neuropathies, specifically Leber's Hereditary Optic Neuropathy (LHON), conditions such as Leber's Congenital Amaurosis, and certain forms of macular degeneration such as Stargardt's

disease, and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 2, 4, 11,13 are rejected under 35 U.S.C. 102(a) as being anticipated by Cavalli et al. (Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin).

Cavalli et al. teaches the use of solid lipid nanoparticles with tobramycin topically to the eye which would inherently result in treatment of any condition susceptible to the tobramycin. The particles had tobramycin at 2.5%w/w, average particle size of 80nm, polydispersity index of 0.12, 0.3mg was administered to each eye in rabbits weighing 2.8-3.5kg.

All the critical elements are taught by the cited reference and thus the claims are anticipated.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 2-4, 7, 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Amselem et al. (U.S. Pat. 5662932).

Amselem et al. teaches pharmaceutical composition comprising emulsomes with a lipid core including solid lipid cores. The particles have a average particle size with preferred range of 10-250nm and in certain preparations the average will fall in the range of 50-150nm. The particles (emulsomes) can be administered in several ways including topically and intravenously. A particular mode of administration described in instillation into the eye and that these compositions are similar to those of parenteral solutions. Several drugs are taught to be used with the particles including beta-adrenergic blockers (e.g. adaprolol and timolol) for glaucoma, antifungal, antibiotics, corticosteroids, AIDS drugs. Examples are provided with drug emulsomes with particles sizes and administered in different modalities were any ophthalmic condition present would inherently be treated (e.g. Example 5 with IV cannabinoid at 0.08mg/kg, Example 6 indomethacin particle size 111+/-32nm ophthalmic use, Example 7 topical indomethacin, Example 12 amphotericin B particle average 107+/-27nm, Example 16-18 adaprolol maleate (0.4%) particle average 89+/-69 to topical to the eye for IOP reduction in rabbit with 2.5-3.0kg, Example 20- IV administration of HU-211 to rates at 5mg/kg particle average 153+/-24nm). It is noted that as the components of the composition are met, the properties of the composition are also met (e.g. polydispersion) (Abstract, Col. 9 line 5-48, Col. 10 line 7-Col. 11line 50, Examples, claims).

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claim 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cavalli et al. (Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin) as applied to claim 2, 4, 11,13 above.

The teachings of Cavalli et al. are addressed above.

Cavalli et al. does not expressly teach the average diameter of the SLN to be between 100 and 200nm. Cavalli does teach tobramycin SLN's where the average particle size of 80nm and fluorescent SLN with an average diameter of 70nm.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to adjust the particle size as desired for the desired size, delivery method, and therapeutic profile; as Cavalli teaches that particle sizes are variable and as the particle sizes are an average, there are particles larger and smaller than 80nm present.

One of ordinary skill in the art would have been motivated to do this because it is desirable to adjust the particle size based on the as desired for the desired size due to the drug, target area, delivery method, and therapeutic profile

14. Claim 7 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cavalli et al. (Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin) as applied to claim 2, 4, 11,13 above, in view of Schwartz (U.S. Pat. 4904649).

The teachings of Cavalli et al. are addressed above.

Cavalli et al. does not expressly teach intravenous delivery or SLN's of the specific drugs in the claim. Cavalli does however teach that many hydrophobic and hydrophilic drugs such as nifedipine, hydrocortisone, tobramycin, timolol, paclitaxel, and doxorubicin have been incorporated into SLN and SLN have been administered by several routes (e.g. parenteral, oral, ocular).

Schwartz teaches that corticosteroids such as hydrocortisone and beta-adrenergic such as timolol are used to treat glaucoma and can be administered in various ways including topically to the eye, orally, intravenously, and iontophoresis (Abstract, Col.5 line 48-52, Col. 6 line 14-33, 44-53).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to incorporate any of the drugs taught as known to be incorporated into SLN's and used intravenously, as suggested by Cavalli and Schwartz, and produce the instant invention. It would have been obvious to one of skill in the art to use any of the rugs taught by Cavalli as known in the art to have been incorporated into SLN such as hydrocortisone in the nanoparticles as Cavalli uses tobramycin (taught as a known drug for SLN's) as an example and used for a known purpose in a known mode of administration as taught by Schwartz.

One of ordinary skill in the art would have been motivated to do this because Cavalli teaches that the SLN's have better therapeutic delivery, release, therapeutic profiles (bioavailability) whereby it would be desirable to use drugs known to be incorporated in to SLN for their known purpose for better results and therapy.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claim 2-4, 7, 11-13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 89 and 91 of copending Application No. 11/62941. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending claims anticipate the broader claims of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

17. Claims 2-4, 7, 11-13 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GIGI HUANG whose telephone number is (571)272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fredrick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH
/Zohreh A Fay/
Primary Examiner, Art Unit 1612